REMARKS

Claims 15-17 are pending in the subject application. Each of claims 15-17 has been amended. The amendments to the claims are completely supported by the application as originally filed and thus they raise no issue of new matter. In particular, support for the amended claims is present, *inter alia*, in the specification as follows: **Claims 15 - 16**: page 19, lines 12-32, page 20, lines 28-32, page 24, lines 1-2, page 26, line 34, page 27, lines 2-4, pages 60-64 and claims 7, 8, 9 and 10 as originally filed; **Claim 17**: page 20, lines 28-31, page 26, line 34 and page 27, lines 2-4. In view of the remarks which follow, applicants respectfully request that the Examiner reconsider and withdraw the rejections made in the February 3, 2003 Office Action.

The Claimed Invention

As recited in claims 15 and 16, the invention is a monoclonal antibody which is or which may be determined, by means of a resonance energy transfer ("RET") assay, to be capable of specifically inhibiting the fusion of a macrophage-tropic primary isolate of HIV-1 to a CD4+ cell susceptible to infection by a macrophage-tropic primary isolate of HIV-1, but not a T cell-tropic isolate of HIV-1 to such CD4+ cell. The subject monoclonal antibody is further capable under identical conditions of (a) specifically inhibiting 67% or greater of fusion of a CD4+ PM-1 cell to a HeLa cell expressing envelope glycoprotein from HIV-1_{JR-FL}, and (b) inhibiting 18% or less of fusion of a CD4+ SUP-T1 cell to a HeLa cell expressing envelope protein from HIV-1_{LAI}, wherein the antibody (i) does not cross-react with HIV-1 envelope glycoprotein or CD4, (ii) reacts with an antigen on the surface of a PM-1 cell, and (iii) does not react with an antigen on the

surface of a SUP-T1 cell.

As recited, moreover, in claim 17, the invention is further directed to a method of inhibiting fusion of a macrophage-tropic primary isolate of HIV-1 with a CD4+ cell susceptible to infection by a macrophage-tropic primary isolate, but not capable of inhibiting fusion of a T cell-tropic isolate of HIV-1 to such CD4+ cell, wherein the method comprises contacting the CD4+ cell with an amount of the above-described monoclonal antibody capable of specifically inhibiting such fusion so as to thereby inhibit such fusion.

Rejection Under 35 U.S.C. 112, First Paragraph - Written Description

The Examiner rejected claims 15-17 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, citing *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981) and *In re Wertheim*, 541, F2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). The Examiner stated that to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonable conclude that the inventor had possession of the claimed invention, citing *Vas-Cath, Inc.*, v. *Mahurkar*, 935, F.2d at 5163, 19 U.S.P.Q.2d at 1116.

The Examiner stated that the issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of antibodies that are capable of inhibiting the fusion of macrophage-tropic HIV-1 isolates to the

appropriate cell targets. As to the Examiner's characterization of the claims as being "broadly directed", however, applicants submit that the claims of their application contain very specific recitations concerning the physical characteristics of the claimed antibodies and thus characterizing these claims as being "broadly directed" is a misnomer.

Further to the above, the Examiner stated that an applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formulas that duly set forth the claimed invention. *Lockwood* v. *American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.A.2d 1961, 1966 (Fed. Cir. 1997).

The facts of the present case are readily distinguishable from those of *Lockwood, supra*, however. Lockwood involved a claim by the appellant that a computerized reservation system utilized by American Airlines infringed several of his patents. The appellant, i.e., Lockwood, contended that the written description of his claimed invention, although it did not describe *in haec verbis* what was claimed in the patents in question, would render the claimed invention obvious to one of ordinary skill in the relevant art. Lockwood alleged, therefore, that he had thus fulfilled the written description requirement with regard to his invention under 35 U.S.C. §112. The Court disagreed, however, holding (at p. 1966) that:

> Lockwood claimed a distinct invention from that disclosed in the specification. It is not sufficient for the purposes of the written description requirement of §112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to the modifications that the inventor might have envisioned but failed to disclose.

No such "speculation" is required in the present case, however, since as demonstrated herein the recitation of the invention set forth in the pending claims is completely supported by the teachings in the application as filed. Thus one skilled in the art would readily conclude, after reviewing applicants' specification, that applicants had possession of the claimed invention at the time their application was originally filed (see, *Vas-Cath, supra, 935 F.2d* at *1563-4, 19 USPQ2d* at *1116*).

The Examiner next stated in the Office Action that the claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation between the structure of the invention and its function. The Examiner stated that a biomolecule sequence described only by functional characteristics, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest, citing *In re Bell*, 991 F.2d 781, 236 U.S.P.Q.2d 1529 (Fed. Cir. 1993). *In re Deuel*, 51 F.3d 1552, 35 U.S.P.Q.2d 1210 (Fed. Cir. 1995).

Applicants believe that the Examiner's reliance upon the above-cited *Bell* and *Duell* decisions is ill-founded, however, since neither of these decisions is directed to, or even addresses, the requirements for a "written description" of a claimed invention under 35 U.S.C. §112, ¶1. In the *Bell* decision, the claims of the application at issue were directed to nucleic acid molecules containing human sequences which code for human insulin-like growth factors I and II (IGF). The Examiner had rejected the claims of the application for obviousness under §103 (which

rejection was affirmed by the Board of Appeals) over a combination of two publications by Rinderknecht disclosing amino acid sequences for IGF-I and -II and a U.S. patent to Weissman et al. which described a general method for isolating a gene for which at least a short amino acid sequence of the encoded protein is known. The applicant appealed the Board's obviousness rejection to the Federal Circuit, which stated (see 991 F.2d 783), "the issue before us is whether the Board correctly determined that the amino acid sequence of a protein in conjunction with a reference indicating a general method of cloning renders the gene *prima facie* obvious." The Court held that the combination did not render the claimed invention obvious and reversed the Board's decision. There is no discussion in the subject decision concerning the sufficiency of the written description of the claimed invention and applicants submit that the decision thus does not support the above-quoted statements attributed to it.

The *Duel* decision involved an application containing claims to DNA and complementary DNA (cDNA) molecules encoding proteins that stimulated cell division. The Examiner rejected the claims as unpatentable for obviousness under §103 and the Board of Patent Appeals and Interferences affirmed the Examiner's decision. The Court reversed the Board's decision, finding that the claimed invention was not obvious over the cited references. In so doing, moreover, the Court specifically declined to address the issue of whether the claims met the requirements of 35 U.S.C. §112. The Court stated (at 51 F.3d 1560), "As this issue [i.e., the satisfaction of the requirements of §112] is not before us, however, we will not address whether claims 4 and 6 satisfy the enablement requirement of §112, first paragraph . . .". It thus also appears that the Examiner's comments are not supported by

the text of the Court's opinion in *Deuel*.

In summary therefore, applicants contend that as neither *Bell* nor *Deuel* address either the written description or the enablement (under 35 U.S.C. §112) of the inventions claimed by the applicants in those cases, these decisions, which are cited by the Examiner in the Office Action as supporting the Examiner's statements on page 2 thereof, do not in fact support those comments.

Further to the above, moreover, even apart from the issue of a lack of support in the cited decisions for the Examiner's statements, applicants assert that their claimed invention is not simply described, "solely in terms of a method of its making coupled with its function . . ." as postulated by the Examiner on page 2 of the Office Action and that the breadth of description of the invention as contained in their specification is significantly more detailed than that. In particular, the Examiner's attention is directed to, e.g., ¶¶ 6-8 of the first Declaration Under 37 C.F.R. §1.132 of Paul J. Maddon, M.D., Ph.D. filed in this case which was executed on March 7, 2002 ("the prior declaration"). Moreover, in addition to the disclosure described in Dr. Maddon's prior declaration relating to methods for identifying and characterizing the presently claimed antibodies, applicants have provided several specific working examples (e.g., the monoclonal antibodies produced by the hybridoma cell lines PA-3, PA-5, PA-6 and PA-7) in Table 3 on page 61. The provision of such "working examples" of antibodies which, as demonstrated by the data provided on p. 61 of applicants' specification, meet the requirements set forth in the claims, strongly supports applicants' contention that their specification contains an adequate written description of the

application as presently claimed which would reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Not only, moreover, are these working examples provided in accordance with the written descriptions of §112, they are recognized by the Examiner as being enabled as well. In the Advisory Action mailed April 8, 2002 in this case, the Examiner stated that, "Appropriately drafted claim language directed toward the specific embodiments set forth (e.g., antibodies produced by PA-3, PA-5, PA-6 & PA-7) would be acceptable.

The Examiner additionally stated in the Office Action (at p. 2) that a lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process, citing *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995). The Examiner stated that the court noted in this decision that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not reasonably lead those skilled in the art to any particular species.

In response, applicants submit that their claims do not provide a "laundry list" as described in the *Fujikawa* decision cited *supra*. Quoting from Dr. Maddon's prior declaration filed in this case (¶8): "The application describes, among other things, the following: a source of an immunogen for eliciting an antibody of the present invention (PM1 cells, page 60, lines 9-11); a method for obtaining an antibody by recovering supernatant from hybridomas generated by immunizing with PM1 cells as the immunogen (page 60, lines 9-13); and a differential screening

assay called the resonance energy transfer ("RET") assay for identifying an antibody having the desired characteristics (pages 30 through 32, line 15). These characteristics include the ability of the antibody to inhibit HIV-1 envelope glycoprotein-mediated membrane fusion using HeLa cells expressing envelope glycoprotein derived from a macrophage-tropic HIV-1 isolate, HIV-1 JR-FL ("HeLa-env JR-FL cells") while not inhibiting HeLa cells expressing envelope glycoprotein derived from a T cell-tropic HIV-1 isolate, HIV-1 LAI ("HeLa-env LAI cells"). Antibodies generated by immunizing with CD4+ PM1 cells inhibited fusion between HeLa-env JR-FL cells and CD4+ PM1 cells (page 60, lines 11-16). This demonstrates that using PM1 or equivalent cells as the immunogen and the RET assay as the differential screening assay, one skilled in the art is able to readily make, identify and select antibodies that have the characteristics of inhibiting fusion between CD4+ PM1 cells and HeLa-env JR-FL cells. Table 3 on page 61 demonstrates that fusion-inhibiting antibodies react with an antigen on the surface of a PM1 cell, do not react with CD4, and do not cross-react with an antigen on the surface of a SUP-T1 cell."

Table 3 on page 61 of the application additionally provides evidence for the recitation in claims 15 and 16 that the monoclonal antibody is further capable under identical conditions of (a) specifically inhibiting 67% or greater of fusion of a CD4+ PM-1 cell to a HeLa cell expressing envelope glycoprotein from HIV-1_{JR-FL}, and (b) inhibiting 18% or less of fusion of a CD4+ SUP-T1 cell to a HeLa cell expressing envelope protein from HIV-1_{LAI}.

Applicants thus submit (as further stated by Dr. Maddon in ¶8 of his prior declaration), that in light of the disclosure contained in applicants' specification, it is apparent that the application

provides detailed guidance for making an antibody and selecting an antibody having the desired characteristics, i.e., those recited in claims 15-16 of the present application.

The Examiner additionally stated in the Office Action (p.3) that an applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. The Examiner stated that an applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, correlation between function and structure, or some combination of such characteristics. The Examiner stated that for some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight. The Examiner stated that the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. The Examiner stated that without such a correlation, the capability to recognize or understand the structure from the mere recitation of function and minimal structure is highly unlikely. The Examiner stated that in the latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 U.S.P.Q.2d 1398, 1404, 1406 (Fed. Cir. 1997), *cert, denied*, 523 U.S. 1089 (1998). *In re Wilder*, 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir. 1984).

The situation with regard to the present invention is readily distinguishable from that found in the *Wilder* decision cited by the Examiner, however. *Wilder* involved an appeal from a decision of the Patent and Trademark Office Board of Patent Appeals and Interferences rejecting generic claims in a reissue application. As support for these claims, the applicant cited the general description of one of the drawings which stated that the apparatus illustrated in the drawing is, "one in which the present invention finds ready application" and also argued that the title of the application was "quite broad". Not surprisingly, the Court determined that the Board's finding that there was an inadequate [written] description of the invention was not clearly erroneous.

In contrast, however, as demonstrated above in the discussion of Dr. Maddon's prior declaration, the present application contains a significant amount of detailed description with regard to preparing, selecting (i.e., through the RET screening assay) and using the presently claimed monoclonal antibodies. Thus applicants submit that the *Wilder* decision is irrelevant to the facts of the present case.

As to the decision in *Regents of the University of California* which as noted above was also cited by the Examiner in support of the remarks on page 3 of the Office Action, applicants have closely reviewed the text of this decision, including the portion (on pps. 1566-1569) dealing with the invalidity of the appellant's U.S. patent No. 4,652,525 ("the '525 patent") on the basis of the written description of the invention contained in the patent specification, and submit that they fail to find any specific support therein for many of the Examiner's remarks as set forth on p. 3 of the Office Action pertaining to methods for satisfying the written description requirements of §112.

Notwithstanding, however, the issue of whether the text of the Court's decision supports the premises for which that decision is cited by the Examiner, applicants submit that the situation with regard to the present invention is readily distinguishable from those involved in the dispute between the Regents of the University of California and Eli Lilly and Co. for the following reasons. The claims of the '525 patent were directed to recombinant DNA technology, i.e., involving recombinant plasmids and microorganisms that produce human insulin. As stated by the Court (at p. 1566):

> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. [citation omitted]. Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." [citation omitted].

In the present case, applicants' claims are not directed to DNA. Rather, claims 15 and 16 are directed to antibodies having certain well-defined physical characteristics, wherein the antibodies may be isolated using a resonance energy transfer (RET) screening assay. Claim 17 relates to a method of use of the antibody recited in claim 16. Applicants submit that they have met their burden of providing a proper written description of the claimed antibodies and method of their use. As pointed out above in the discussion of ¶8 of Dr. Maddon's prior declaration under 1.132, the application describes, *inter alia*, a source of an immunogen for eliciting an antibody of the present invention; a method for obtaining an antibody by recovering supernatant from hybridomas generated by immunizing with the immunogen; and a differential screening assay (the RET assay) for identifying an

antibody having the desired characteristics. As the subject disclosure thus correlates with the recitations concerning the antibodies in the presently pending claims, applicants submit that they have fulfilled their burden under 35 U.S.C. §112, ¶1 to provide an appropriate written description of the invention as presently claimed.

Further to the above, according to M.P.E.P. §2163.04 (I), in rejecting a claim for lack of an appropriate written description, the Examiner must set forth express findings of fact which support the lack of written description conclusion. These findings should (A) identify the claim limitation in issue; and (B) establish a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor(s) was in possession of the invention as claimed in view of the disclosure of the application as filed. These M.P.E.P. guidelines are in accordance with the Court's decision in *In re Oetiker, 977 F.2d 1443 (Fed. Cir. 1992)* wherein the Court held (see p. 1445) that the Examiner bears the initial burden of presenting a *prima facie* case for unpatentability for an alleged lack of written description of the claimed invention. As stated by the Court of Customs and Patent Appeals in *In re Wertheim, 541 F.2d 257, 262-3 (CCPA 1976)* the Examiner's burden is discharged by presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined in the claims.

With regard to the above requirement, the Examiner stated, without identifying any source in support therefore, that certain factors are to be considered in determining whether there is sufficient evidence of possession, including the level of skill and knowledge in the art, partial structure, physical and/or

chemical properties, functional characteristics alone or coupled with a known to disclosed correlation between structure and function, and the method of making the claimed invention. As to these factors, applicants have previously pointed out that the level of skill necessary to make the antibodies of the invention was relatively low, i.e., a laboratory technician with a Bachelor's degree and one to two years of experience working with hybridomas (see, e.g., the prior Maddon declaration at ¶7). In addition, applicants' disclosure describes a variety of physical properties of the claimed antibodies, which properties, moreover, are demonstrated in the antibodies produced in the working examples (i.e., through the use of hybridomas PA-3, PA-5, PA-6 and PA-7). Moreover, as described, e.g., in ¶8 of the prior Maddon declaration, the method of making the antibodies recited in the claims is specifically set forth in applicants' specification, as are the details concerning the resonance energy transfer screening assay for identifying antibodies made by the disclosed processes which have the properties recited in the claims. For all of these reasons, therefore, applicants submit that weighing the factors as above described which, according to the Examiner, are to be considered in determining whether a proper written description has been provided, the scale tips decidedly in favor of a finding that the written description provided by applicants meets the requirements therefore under §112, ¶1.

Further with regard to the above factors, the Examiner stated on page 4 of the Office Action that the disclosure (see p. 60) describes the isolation and preparation of four hybridomas (designated PA-3, -5, -6, and -7) that secrete antibodies that are capable of inhibiting HeLa-env_{JR-FL} fusion to PM1 cells in an in vitro RET assay. The Examiner then stated that, however, no

detailed structural or functional characterizations of the monoclonal antibodies produced by these hybridomas were provided. The Examiner additionally stated that no detailed structural characterization was performed pertaining to the antigenic determinant recognized by said hybridoma supernatants. The Examiner stated that thus, the binding specificity and coding potential of the antibodies has not been clearly ascertained. The Examiner stated that the skilled artisan would reasonably conclude that applicants were in possession of these four hybridomas. The Examiner stated that, however, the binding specificity of these antibodies remains to be elucidated. The Examiner stated that thus, it is not readily manifest if these antibodies have the claimed characteristics (e.g., inhibition of macrophage-tropic virus fusion without inhibiting T-cell-tropic isolates). The Examiner stated since the disclosure fails to provide adequate guidance pertaining to the structure of the claimed antibodies, the structure of the recognized antigenic determinants, and a reproducible method for making antibodies with the desired phenotype, inadequate written support exists for the claimed invention.

In response to the Examiner's comments as to the lack of disclosure relating to structural characteristics of the claimed antibodies and/or the recognized antigenic determinants, the Examiner's attention is respectfully directed to ¶¶9-11 of the prior Maddon declaration. Dr. Maddon stated in ¶9 of his prior declaration that it is <u>not necessary</u> for one of ordinary skill in the art to know the antigenic determinants or epitopes on the surface of the whole cells used for immunization or their structural configuration in order to make an antibody having the characteristics of the antibody claimed in the present invention. Dr. Maddon additionally stated that it is well-established that having a starting immunogenic source such as an immunogenic whole

cell and following standard immunization methods, a series of antibodies will be elicited. Dr. Maddon then further stated in his declaration that it is also well-established that the [RET] screening method allows one skilled in the art to identify and select antibodies having the desired characteristics. Dr. Maddon thus concluded (see ¶9) that one of ordinary skill in the art using the screening methods disclosed in the subject application would readily obtain an antibody having the characteristics recited in the claims to the present invention.

Moreover, as additionally stated at ¶10 of Dr. Maddon's prior declaration, he and his colleagues have produced, in addition to the four working examples disclosed in the specification of the present application (i.e., PA-3, PA-5, PA-6 and PA-7) a number of additional antibodies that were found to inhibit HIV-1 envelope-mediated fusion between HeLa-env_{JR-FL} cells and CD4+ cells, i.e., PM-1 cells, in a RET assay. As further stated in ¶10, the results were reported in the Journal of Virology, May 1999, p. 4145-4155 and a copy of the article was attached as Exhibit 3 to the subject declaration. As pointed out in ¶10 of the prior declaration, the reference discloses that of 10,000 hybridoma supernatants screened in the RET assay, over 100 inhibited fusion by greater than 50%. Moreover, six antibodies positive in the RET assay, designated therein as PA8, PA9, PA10, PA11, PA12 and PA14 were further characterized and were determined to bind to an antigen which is found on the surface of the macrophage cell line PM-1. Dr. Maddon thus concluded, as stated in ¶11 of his prior declaration, that the present specification provides sufficient teaching to one skilled in the art to readily enable making, screening and selecting antibodies that meet the requirements of the present invention without any undue experimentation.

Moreover, further in support of the contention that it is not necessary for one of ordinary skill in the art to know the antigenic determinants or epitopes on the surface of the whole cells used for immunization, or their structural configuration in order to make an antibody having the characteristics of an antibody claimed in the present invention is a "Supplemental Declaration Under 37 C.F.R. §1.132 of Paul J. Maddon, M.D., Ph.D." ("the supplemental Maddon declaration") attached hereto as **EXHIBIT 1.** The supplemental declaration states (¶6) that it is irrelevant to both the amount and level of experimentation needed to produce the claimed antibodies whether one skilled in the art has knowledge of the specific structure of the immunogenic or antigenic determinants of an immunogen, or of the physical structure of the claimed antibody. Dr. Maddon further stated in his supplemental declaration that the claimed monoclonal antibodies could be produced in the same manner whether or not one had knowledge of such structure of the determinants on the immunogen and/or structure of the antibody. Dr. Maddon then went on to state that with or without such knowledge one could (i) immunize mice with the immunogen taught in the specification comprising the appropriate immunogenic/antigenic determinants, i.e., PM-1 cells; (ii) generate hybridomas upon such immunization; (iii) obtain antibodies by recovery of supernatant from such hybridomas; and (iv) subject such antibodies to a differential screening assay known as a resonance energy transfer (RET) assay to identify antibodies having the claimed fusion-inhibiting characteristics.

Dr. Maddon further stated in the supplemental declaration that the above steps are carried out in the same manner whether or not the antigenic determinants and the antibody structure are known. Dr. Maddon stated that the essential teaching for obtaining monoclonal antibodies as claimed has been provided by the

specification by identifying the proper immunogen having the appropriate antigenic determinants, i.e., PM-1 cells or equivalent cells, for eliciting the antibody along with the differential screening assays for selecting monoclonal antibodies meeting the physical criteria set forth in the claims. Dr. Maddon thus concluded (see ¶6 of the supplemental declaration) that a lack of structural information concerning the antigenic determinants and the monoclonal antibodies would not necessitate any experimentation by one skilled in the art beyond that which would be required were such immunogenic or antigenic determinants known.

It is thus applicants' contention that the specific structure of the immunogenic or antigenic determinants of the immunogen, or of the physical structure of the claimed monoclonal antibody need not be shown in order for the invention to be adequately described. That is, chemical structure is only one of several parameters that may be used to describe a material. In this regard, Dr. Maddon stated in ¶7 of his supplemental declaration that, to his knowledge, it is common for those working in the field of monoclonal antibodies to characterize the antibodies in terms of their physical characteristics, such as function, without needing to characterize such antibodies in terms of their polypeptide structure or the structural identity of their immunogenic or antigenic determinants.

Dr. Maddon then further stated in ¶7 that a representative example of such characterization is provided by U.S. Patent No. 4,381,295 to Kung et al. ("the '295 patent"). A copy of the '295 patent is attached as Exhibit A to Dr. Maddon's supplemental declaration. As further stated by Dr. Maddon, the '295 patent does not describe the antibody which is the subject of the

invention in terms of either determinants or structure. Rather, as demonstrated by the '295 patent claims, the antibody is described in terms of its binding reactivity and the method by which the antibody is made.

Dr. Maddon then went on to state in ¶8 of his supplemental declaration, that the practice of describing an antibody by its physical characteristics, such as its function rather than by polypeptide structure, extends as well to methods of using antibodies. U.S. Patent No. 5,993,816 to Lederman et al. ("the '816 patent") is attached as Exhibit B to Dr. Maddon's supplemental declaration. Dr. Maddon stated that the '816 patent contains claims to a method of inhibiting a humoral response by contacting T cells with an antibody, wherein the antibody is not described in terms of its structure, but rather it is claimed in terms of its binding characteristics.

Dr. Maddon therefore concluded in ¶10 of his supplemental declaration, that the present application would permit one skilled in the field of making antibodies to make and use the antibodies as presently claimed. This conclusion is completely supported by the facts provided in the first and second declarations of Dr. Maddon provided in this case, which declarations are entitled to be accorded evidentiary weight.

Applicants, moreover, respectfully traverse the above-quoted statement by the Examiner (from page 4 of the Office Action) that it is not "readily manifest" if applicants' antibodies have the claimed characteristics. In response, applicants submit that the data presented, e.g. at pps. 60-61 of the application clearly manifests that the antibodies produced from the hybridomas PA-3, PA-5, Pa-6 and PA-7 meet the recitations of the claims in that they inhibit macrophage-tropic virus fusion without inhibiting T

cell-tropic isolates. Applicants additionally take exception to, and thus traverse, the Examiner's statement (also on p. 4 of the Office Action) that their disclosure fails to provide a "reproducible method for making antibodies with the desired phenotype". In response, they respectfully submit that the working examples which they have provided clearly demonstrate that their specification teaches a reproducible method for making antibodies with the desired phenotype.

For all of the reasons set forth above, therefore, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 15-17 based on an alleged lack of an appropriate written description of the claimed invention under 35 U.S.C. §112, ¶1.

Rejection Under 35 U.S.C. §112, First Paragraph - Enablement

The Examiner also rejected claims 15-17 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In response to the Examiner's rejection, applicants respectfully traverse for the reasons set forth below.

The Examiner stated that the claims are broadly directed toward antibodies that are capable of inhibiting macrophage-tropic HIV-1 isolate fusion to a suitable target cell without inhibiting T-cell-tropic isolate fusion to a suitable target cell. Applicants respectfully traverse the characterization of their claims as being "broadly directed". Claims 15 and 16 as now amended, and claim 17 which depends from claim 16 and thus includes all of the

recitations of that claim, contain very specific recitations concerning the physical characteristics of the presently claimed antibodies. These physical characteristics, as demonstrated in the discussion above, are clearly set forth in the written description of the invention provided by the specification of the present application. Thus applicants' claims fulfill the "written description" requirement under 35 U.S.C. §112. For the reasons which follow, the invention as presently claimed also meets the requirements for enablement under §112.

The Examiner additionally stated that the disclosure describes the isolation and preparation (see p. 60) of four hybridomas (designated PA-3, PA-5, PA-6, and PA-7) that secrete antibodies that are capable of inhibiting HeLa-env_{JR-FL} fusion to PM1 cells in an *in vitro* RET assay. The examiner stated however, no detailed structural or functional characterizations of the monoclonal antibodies produced by these hybridomas were provided. The Examiner stated that no detailed structural characterization was performed pertaining to the antigenic determinant recognized by said hybridoma supernatants. The Examiner stated that thus, the binding specificity and coding potential of the antibodies has not been clearly ascertained.

The Examiner stated that the legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C.1998) and *Ex Parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). Applicants note that, as stated in *Forman, supra* (at p. 547), "The 'undue experimentation' prescription is, in effect, a gloss on the statute [i.e., "undue experimentation" is not specifically mentioned anywhere in 35 U.S.C. §112] which has arisen from

decisional law which requires that sufficient information be given in the application so that one of ordinary skill in the art can practice it without the necessity for undue experimentation (citations omitted)." The *Wands* decision (at page 1404) quotes from *Forman, supra* in setting forth several factual inquiries which should be considered when assessing whether "undue experimentation" is necessary to practice the invention. The Examiner stated that these factors include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in that art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims, citing *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965).

The Examiner then further stated that applicants' disclosure fails to provide adequate guidance pertaining to a number of the above considerations [nos. 1-8] as follows:

1) The Examiner stated that the disclosure fails to provide adequate guidance pertaining to the structural requirements of any given antibody. The Examiner stated that antibodies are large and complex molecules comprised of two ~55 kDa heavy chain polypeptides and two ~25 kDa light chain polypeptides (Frazer and Capra, 1999). The Examiner stated that within each chain are relatively constant regions and highly variable regions. The Examiner stated that it is the highly variable regions of these molecules that dictate many of the functional properties of the antibody such as antigen binding specificity. The Examiner stated that however, it is well-known in the art that antibody structure is highly variable due to the genetic diversity of the antibody locus (Max, 1999). The Examiner stated that that the

recombinatorial events involved in antibody production can produce 32 million different combinations. The Examiner stated that thus, the skilled artisan cannot predict what the structure of any given antibody will be.

2) The Examiner stated that the disclosure fails to provide any guidance pertaining to the structure of the antigenic determinants recognized by the antibodies of interest. The Examiner stated that antibody-antigen binding interactions generally involve between five to eight amino acids. The Examiner stated that however, single amino acid changes the antigenic determinant can drastically reduce of completely abrogate antigen-antibody binding (Mateu et al., 1992; Alexander et al., 1992). The Examiner stated that thus, in order to reproducibly generate antibodies with the desired characteristics, the skilled artisan would require knowledge of the antigenic determinants modulating this interaction. The Examiner stated that however, the specification is silent pertaining to this point.

3) The Examiner stated that the disclosure fails to provide a reproducible method for making antibodies with the claimed specificity. The Examiner stated that as noted *supra* in points one and two, there is considerable unpredictability pertaining to the generation of antibodies with the desired properties and characteristics. The Examiner stated that while the specification provides a generic method for producing antibodies, it fails to provide any reproducible methodologies for obtaining antibodies with the desired characteristics.

4) The Examiner stated that the claims are broadly directed toward a large genus of antibodies without providing sufficient structural and functional support pertaining to the properties of said antibodies.

5) The Examiner stated that the disclosure fails to provide a sufficient number of working embodiments. The Examiner stated that while four hybridomas were generated, the precise structural and functional characteristics of these antibodies were never clearly set forth.

6) The Examiner stated that the prior art is unpredictable and fails to provide any guidance pertaining to those macrophage-tropic-specific immunogenic/antigenic determinants that can be used to produce antibodies with the desired binding specificity. The Examiner stated that as noted *supra* in points one and two, considerable unpredictability was present in the art at the time of filing. The Examiner stated that however, the disclosure fails to address any of these concerns.

7) The Examiner stated that legal precedence dictate that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification. *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). *In re Vaeck*, 20 U.S.P.Q.2d 1438 (C.A.F.C. 1991). *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976).

The Examiner stated that thus, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

In response to these comments by the Examiner, applicants reiterate their contention, noted above, that it is not necessary for one of ordinary skill in the art to know the antigenic determinants or epitopes on the surface of the whole cells used for immunization or their structural configuration in order to

make an antibody having the characteristics of an antibody claimed in the present invention. This view, moreover, is completely supported by ¶¶9-11 of Dr. Maddon's prior declaration for the reasons presented above in the discussion of the rejection based on the written description of the invention. Moreover, as additionally explained above, Dr. Maddon's supplemental declaration (Exhibit 1 hereto) further demonstrates that it is irrelevant to both the amount and level of experimentation needed to produce the claimed antibodies whether one skilled in the art has knowledge of the specific structure of the immunogenic or antigenic determinants of an immunogen, or of the physical structure of the claimed antibody. Thus as demonstrated by Dr. Maddon in his supplemental declaration a lack of structural information concerning the antigenic determinants and the monoclonal antibodies would not necessitate any experimentation by one skilled in the art beyond that which would be required were such immunogenic or antigenic determinants known, since the claimed monoclonal antibodies would be produced in the same manner whether or not one had knowledge of such structure of the determinants on the immunogen and/or the structure of the antibody. Thus one of ordinary skill at the time the application was filed would readily be able to prepare, select and use an antibody having the characteristics recited in the present claims without any excess or undue experimentation.

The Examiner stated that the applicants traverse and argue that claims are fully enabled. The Examiner stated that a declaration was provided under 37 C.F.R. §1.132 by Dr. Paul J. Maddon in support [i.e., the prior declaration]. The Examiner stated that Dr. Maddon asserted that methods for preparing the antibodies of interest were available at the time of filing. The Examiner stated that the Examiner does not dispute the finding that generic methods of preparing and isolating antibodies were

available. The Examiner stated that the problem is that a reproducible method that produces antibodies with the specifically claimed characteristics was not provided and that there is considerable uncertainty pertaining to the generation of antibodies as set forth *supra*.

Applicants respectfully submit that the Examiner's argument is not supported by the facts as demonstrated herein and as supported by the two declarations of Dr. Paul Maddon under 37 C.F.R. §1.132. That is, applicants' specification clearly teaches a method comprising (i) immunizing mice with an immunogen comprising appropriate immunogenic/antigenic determinants, i.e., PM-1 cells; (ii) generating hybridomas upon such immunization; (iii) obtaining antibodies by recovery of supernatant from such hybridomas; and (iv) subjecting such antibodies to the differential screening assay known as a resonance energy transfer (RET) to identify antibodies having the claimed fusion-inhibiting characteristics (see, e.g. Maddon supplemental declaration, ¶6). This is, moreover, the methodology used to obtain the four working examples (i.e., PA-3, PA-5, PA-6 and Pa-7) described at pps. 60-61 of the specification. The data provided in Table 3 on page 61 clearly demonstrates that the subject antibodies, produced in the manner described in applicants' specification, exhibit the physical characteristics recited in the claims. Furthermore, the Examiner has not pointed to anything in applicants' specification, or in the prior art, which would indicate that applicants could not use the above-described methodology to make additional antibodies which exhibit the presently claimed characteristics. In fact, as discussed in ¶10 of Dr. Maddon's prior declaration, Dr. Maddon specifically described "that using methods described in the present specification" he and his colleagues made over 100 additional

antibodies that inhibited HIV-1 envelope-mediated fusion between HeLa-env_{JR-FL} cells and the CD4+ cells, PM-1 cells by greater than 50%. These results were reported in the *Journal of Virology* article attached as Exhibit 3 to Dr. Maddon's prior declaration. These experimental results provide a clear indication of the reproducibility of applicants' method for preparing antibodies as recited in the present claims. Applicants thus respectfully submit that the Examiner is incorrect in his assessment of the disclosure as contained in their application.

The Examiner then went on to state that since the disclosure fails to identify the immunogenic/ antigenic determinant(s) of interest and the structure of any given antibody, the skilled artisan has been extended an undue invitation to further experimentation. In response, applicants reiterate that for the reasons set forth in the two declarations of Dr. Maddon discussed in detail above, it is not necessary for one of ordinary skill in this art to know the immunogenic/antigenic determinants or the structure of the antibody(ies) exhibiting the physical properties set forth in the claims in order to practice the presently claimed invention. Those arguments are specifically incorporated by reference herein and thus are not repeated again here. The Examiner then stated that moreover, the claims are directed toward a specific chemical compound (e.g., antibody) with defined structure and binding characteristics. In response to this statement applicants note that as pointed out herein, applicants have elected, as is their right, to define their invention in the most appropriate manner, i.e., in terms of its properties, not its structure. Dr. Maddon's supplemental declaration demonstrates in ¶7 and ¶8 that this is not an unusual practice in the antibody art. Applicants thus respectfully reiterate their argument that the details concerning structure are unnecessary under the present circumstances for defining the invention discovered by

applicants.

The Examiner stated that the declaration provided by Dr. Maddon [i.e., the prior declaration executed March 7, 2002] fails to address these caveats. The Examiner stated that it only discloses generic methods of preparation and fails to provide any further illumination pertaining to the immunogenic/antigenic determinants modulating the antigen/antibody binding interactions and fails to provide any guidance pertaining to the structure of any given antibody.

Applicants submit, however, that the manner of the Examiner's response to the prior declaration submitted by Dr. Maddon does not meet the requirements set forth by the Federal Circuit's decision in *In re Alton, 76 F.3d 1168* which deals, *inter alia*, with the requirements for responding to such declarations by an Examiner. In *Alton*, the applicant had provided an evidentiary declaration of one skilled in the art under 37 C.F.R. 1.132 ("the Wall declaration") to support his contention that the specification of the application contained a sufficient written description of the claimed invention. The Examiner, and later the Board of Appeals, gave no weight to the declaration, characterizing it (at p. 1171) as being "[a]n opinion affidavit on the ultimate legal question at issue" and thus provided no rebuttal to the points raised in the declaration.

The Federal Circuit, however, held that the Examiner had erred in summarily dismissing the declaration without an adequate explanation of why the declaration failed to rebut the *prima facie* case of inadequate description.

Applicants submit, therefore, that the Examiner is required to rely upon more than just his opinion in traversing the points

raised by Dr. Maddon in his declaration. That is, the Examiner must point to some tangible source, i.e., a patent, treatise, journal article, etc. to "disprove" the contentions set forth in the declaration. Applicants contend that the Examiner has not met this burden and thus has not overcome the declaration.

Moreover, in the specific context of declarations submitted under 1.132 to establish enablement, M.P.E.P. §2164.05 states:

> The examiner must . . . weigh all the evidence before him . . ., including the specification and any new evidence supplied by the applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should **never** make the determination based on personal opinion. The determination should always be based on the weight of all of the evidence (emphasis in original).

Applicants submit, however, that the Examiner has relied herein on his own opinion of how matters stand in the art to counter the points raised in the Maddon declaration. He did not, as required, provide any evidence to support his arguments concerning the statements made by Dr. Maddon. Applicants therefore respectfully submit that the Examiner has not carried his burden of overcoming the evidence provided by Dr. Maddon's prior declaration which, when taken in conjunction with Dr. Maddon's supplemental declaration submitted herewith, completely supports applicants' contention that the teachings in the present specification meet all of the requirements for (1) providing an appropriate written description and (2) enabling the presently claimed invention.

Summary

For all of the reasons set forth hereinabove, applicants submit that the invention recited in claims 15-17 is described in the specification in such a way as (1) to reasonably convey to one skilled in the art that, at the time the application was first

filed, the applicants had possession thereof, and (2) to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same. As such, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection and earnestly solicit allowance of the now pending claims 15-17 as amended.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants invite the Examiner to telephone their attorneys at the number provided below.

No fee, other than the enclosed $465.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this response and a check for the indicated amount is enclosed. However, should any other fee be required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Mark A Farley

John P. White
Registration No. 28,678
Mark A. Farley
Registration No. 33,170
Attorneys for Applicant(s)
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Mark A Farley 8-4-03

John P. White Date
Reg. No. 28,678
Mark A. Farley
Reg. No. 33,170